

**REMARKS**

Claims 1-8 are pending in this application. Claims 9-13 are cancelled without prejudice.

As a preliminary matter, the Office Action repeatedly refers to SEQ ID NO: 1 as a limitation of the present claims. Applicants assume that this is a typographical error in the Office Action, since the present claims refer to SEQ ID NO: 2, not to SEQ ID NO: 1. The arguments presented below are made on the assumption that all references to SEQ ID NO: 1 were intended to refer to SEQ ID NO: 2.

**All of the Present Claims are Entitled to an August 14, 1998 Priority Date.**

The Office Action indicated that an English language translation of the German priority application and a declaration under Rule 132 could be used to overcome rejections based on the Zabel *et al.* reference. Submitted herewith is a certified English translation of the German priority Application DE 198 37 015.6. The text of the translated priority application is substantially the same as the text of the present application. Accordingly, all of the present claims are amply supported by the priority application and are entitled to a priority date of August 14, 1998.

The "Declaration Under 37 CFR 132" by inventor Ulrike Zabel, submitted herewith states that Dr. Zabel is a coinventor of the invention described in the present application, along with Harald Schmidt and Wolfgang Poller. Dr. Zabel further states that she and Harald Schmidt were coauthors of Zabel *et al.*, along with Monica Wagner and Mylinh La. As attested in the Declaration, Monica Wagner was an assistant who worked under the direction of Dr. Zabel and Mylinh La was a student who worked under the guidance of Dr. Schmidt. Neither Monica Wagner nor Mylinh La made an inventive contribution to the claims of the present application. Zabel *et al.* is the work of the present inventors and was published after the priority date of the present application. Accordingly, Zabel *et al.* is not available as a reference against the present claims.

**Claims 1 and 2 Are Not Anticipated by the Applied References.**

Claim 1 has been rejected as allegedly being anticipated by Giuli *et al.* This rejection is unwarranted and should be withdrawn. Claim 1 is directed to an isolated human guanylyl cyclase  $\alpha 1/\beta 1$  protein, which is an enzymatically active heterodimer comprising hsGC $\alpha 1$  (having the amino acid sequence of SEQ ID NO: 2) and hsGC $\beta 1$  (having the amino acid sequence of SEQ ID NO: 4). Although Giuli *et al.* purport to describe certain  $\alpha$  and  $\beta$

subunits of human guanylyl cyclase, the reference does not describe an enzymatically active heterodimer of hsGC $\alpha$ 1 (SEQ ID NO: 2) and hsGC $\beta$ 1 (SEQ ID NO: 4). In fact, the sequence for the  $\alpha$  chain reported by the reference (see Fig. 2 of Giuli *et al.*) is not the same sequence as SEQ ID NO: 2 of the present application. The amino acid sequence for the  $\alpha$  chain in Fig. 2 of Giuli *et al.* includes 717 amino acid residues, whereas SEQ ID NO: 2 includes only 690 residues. Thus, the protein structure reported by Giuli, *et al.* is not the same as the isolated protein of the present claims. Sequence in Fig. 2 of Giuli *et al.* includes a number of specific sequence differences from SEQ ID NO: 2 beginning with amino acid residue 124 and continuing through the end of the sequence. Accordingly, Giuli *et al.* does not teach or suggest the isolated human guanylyl cyclase  $\alpha$ 1/ $\beta$ 1 protein that is presently claimed.

The specific sequence differences between SEQ ID NO: 2 and the Giuli *et al.* sequence are also highlighted in Gencore sequence matching printout for "Result 1" included with the Office Action. In this printout the differences between the database sequence and the Giuli *et al.* sequence are listed as "CONFLICTS". The sequence in the database clearly is NOT the same sequence as reported by Giuli *et al.* in Fig. 2. Furthermore, Giuli *et al.* isolated and sequenced a DNA molecule, not a protein. The present claims are directed to an isolated protein. Clearly, Giuli *et al.* does not disclose an isolated protein having the amino acid residue sequence of SEQ ID NO: 2, and thus, does not disclose all of the limitations of claim 1. Accordingly, Giuli *et al.* cannot anticipate claim 1 of the present application.

The Gencore printout bearing a date of July 2, 2003 also shows that the database sequence, for which the Examiner obtained a 100% match with SEQ ID NO: 2, was modified on May 30, 2000, which is after the priority date of the present application. Thus, this database sequence cannot be used as a reference against the present application. A copy of the Genecore printout with the relevant portions underlined, and a copy of page 85 of Giuli *et al.* with the sequence differences underlined, are attached hereto as Appendix I and Appendix II, respectively, for the convenience of the Examiner.

Claim 1 and 2 were also rejected as being anticipated by Zabel *et al.* Since Zabel *et al.* is not available as a reference against this application, this ground for rejection is moot.

**Claims 3-8 Are Not Obvious Over the Applied References.**

Claims 3-8 have been rejected as purportedly being obvious over either Zabel *et al.* or Giuli *et al.* and further in view of common knowledge in the art regarding methods of affinity chromatography using affinity tags for protein purification. This rejection is also

unwarranted, and is hereby traversed. As noted above, Zabel *et al.* is not available as a reference against the present application. Giuili *et al.* does not teach or suggest an isolated protein having the amino acid residue sequence of SEQ ID NO: 2 as explained hereinabove, which is a material limitation of all of the claims. Accordingly, even assuming common knowledge regarding purification using affinity tags, the combination of Giuili *et al.* with such common knowledge cannot and does not render claims 3-8 obvious. The issue here is not purification, but rather whether or not the claimed isolated protein would have been obvious to one of ordinary skill in the art. A *prima facie* case for obviousness has not been established. The obviousness rejection cannot stand.

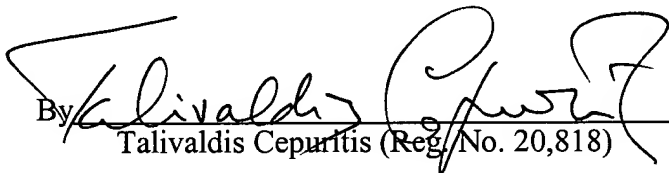
**Conclusion.**

All of the present claims are deemed to be patentable over Giuili *et al.*  
Reconsideration and entry of this amendment are earnestly solicited. In the event that the foregoing is not deemed persuasive, Applicants request that this amendment be entered to place the application in better form for appeal.

Respectfully submitted,

Dated August 2, 2004

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Application No. 09/762,767

Amendment Dated: August 2, 2004

#### APPENDIX I

Pages 1 and 2 of Gencore Search Report labeled "us-09-762-767a-2.rsp" (provided with the Office Action), with underlining added by Applicants to point out significant information in the report relating differences between the database sequence and the sequence of Giuili *et al.*

GenCore version 5.1.6  
Copyright (c) 1993 - 2003 Compugen Ltd.

OM protein - protein search, using sw model

Run on: June 27, 2003, 12:55:07 ; Search time 11.0695 Seconds  
(without alignments)  
2585.358 Million cell updates/sec

Title: US-09-762-767A-2

Perfect score: 3593

Sequence: 1 MFCTKLKDLKITGCPFSLL.....QKKDVEDGNANFLGKASGID 690

Scoring table: BLOSUM62  
Gapop 10.0 , Gapext 0.5

Searched: 112892 seqs, 41476328 residues

Total number of hits satisfying chosen parameters: 112892

Minimum DB seq length: 0

Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%

Maximum Match 100%

Listing first 45 summaries

Database : SwissProt\_40.\*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	Query Match	Length	ID	Description
1	3593	100.0	690	1 CYG3_HUMAN	Q02108 homo sapien
2	3232	90.0	690	1 CYG3_RAT	P19686 rattus norv
3	3107	86.5	691	1 CYG3_BOVIN	P19687 bos taurus
4	1651	46.0	730	1 CYG4_RAT	Q94V14 rattus norv
5	1635	45.5	732	1 CYG4_HUMAN	P33402 homo sapien
6	976.5	27.2	683	1 CYGH_DROME	Q07093 drosophila
7	795	22.1	619	1 CYG1_RAT	P20595 rattus norv
8	793.5	22.1	619	1 CYG1_BOVIN	P16068 bos taurus
9	789.5	22.0	619	1 CYG1_HUMAN	Q02153 homo sapien
10	774.5	21.6	682	1 CYG2_RAT	P22717 rattus norv
11	708	19.7	617	1 CYG2_HUMAN	O75343 homo sapien
12	460	12.8	1047	1 ANPB_BOVIN	P46197 bos taurus
13	460	12.8	1047	1 ANPB_HUMAN	P20594 homo sapien
14	460	12.8	1047	1 ANPB_RAT	P16067 rattus norv
15	457.5	12.7	1057	1 ANPA_RAT	P18910 rattus norv
16	456.5	12.7	1061	1 ANPA_HUMAN	P16066 homo sapien
17	454.5	12.6	1057	1 ANPA_MOUSE	P18293 mus musculu
18	452	12.6	433	1 ASGC_RAT	P55205 rattus norv
19	450	12.5	1108	1 CYGE_MOUSE	P52785 mus musculu
20	448	12.5	1108	1 CYGE_RAT	P51840 rattus norv
21	445	12.4	1109	1 CYGD_CANFA	O19179 canis fami
22	442	12.3	1109	1 CYGF_HUMAN	P51841 homo sapien
23	440	12.2	1103	1 CYGF_BOVIN	Q02740 bos taurus
24	438	12.2	1108	1 CYGF_RAT	P51842 rattus norv
25	438	12.2	1110	1 CYGD_BOVIN	P55203 bos taurus
26	434	12.1	1103	1 CYGD_HUMAN	Q02846 homo sapien
27	430	12.0	1110	1 CYGX_RAT	P51839 rattus norv
28	428.5	11.9	1050	1 ANPB_ANGJA	P55202 anguilla ja
29	427	11.9	1125	1 CYGS_STRPU	P16065 strongyloce
30	414.5	11.5	1073	1 HSER_PIG	P55204 sus scrofa
31	408.5	11.4	1073	1 HSER_HUMAN	P25092 homo sapien
32	407.5	11.3	1072	1 HSER_RAT	P23897 rattus norv
33	399.5	11.1	1076	1 HSER_CAVPO	P70106 cavia porce

RESULT 1  
CYG3\_HUMAN

ID	CYG3_HUMAN	STANDARD;	PRT;	690 AA.
AC	Q02108; O43843;			
DT	01-JUL-1993 (Rel. 26, Created)			
DT	30-MAY-2000 (Rel. 39, Last sequence update)			
DE	16-OCT-2001 (Rel. 40, Last annotation update)			
DE	Guanylate cyclase soluble, alpha-1 chain (EC 4.6.1.2) (GCS-alpha-1)			
DE	(Soluble guanylate cyclase large subunit) (GCS-alpha-3).			
GN	GUCY1A1 OR GUCY1A3 OR GUCY1A3 OR GUCY1A3			
OS	Homo sapiens (Human).			
OC	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;			
OC	Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.			
OX	NCBI_TaxID=9606;			
RN	[1]			
RP	SEQUENCE FROM N.A.			
RC	TISSUE=Brain;			
RX	MEDLINE=923116204; PubMed=1352257;			
RA	Giulivi G., Scholl U., Bulle F., Gueliaen G.;			
RT	"Molecular cloning of the cDNAs coding for the two subunits of			
RT	soluble guanylate cyclase from human brain.";			
RL	FEBS Lett. 304:83-88(1992).			
RN	[2]			
RP	SEQUENCE FROM N.A.			
RC	TISSUE=Kidney;			
RA	Gansmans Y., Brouckaert P., Fiers W.;			
RT	"Human soluble guanylate cyclase large subunit mRNA, alpha3-like.";			
RL	Submitted (MAY-1996) to the EMBL/GenBank/DBJ databases.			
RN	[3]			
RP	SEQUENCE FROM N.A.			
RC	TISSUE=Brain;			
RX	MEDLINE=98416113; PubMed=9742212;			
RA	Zabel U., Weeger M., La M., Schmidt H.H.;			
RT	"Human soluble guanylate cyclase: functional expression and revised			
RT	isoenzyme family.";			
RL	Biochem. J. 335:51-57(1998).			
CC	-!- CATALYTIC ACTIVITY: GTP -> 3',5'-cyclic GMP + diphosphate.			
CC	-!- ENZYME REGULATION: ACTIVATED BY NITRIC OXIDE IN THE PRESENCE OF			
CC	MAGNESIUM OR MANGANESE IONS.			
CC	-!- SUBUNIT: HETERO-DIMER OF AN ALPHA AND A BETA CHAIN.			
CC	-!- SUBCELLULAR LOCATION: Cytoplasmic.			
CC	-!- MISCELLANEOUS: THERE ARE TWO TYPES OF GUANYLATE CYCLASES: SOLUBLE			
CC	FORMS AND MEMBRANE-ASSOCIATED RECEPTOR FORMS.			
CC	-!- SIMILARITY: BELONGS TO ADENYLATE CYCLASE CLASS-4/GUANYLYL CYCLASE			
CC	FAMILY.			
CC	-----			
CC	This SWISS-PROT entry is copyright. It is produced through a collaboration			
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CC	-----			
DR	EMBL; X65534; CAA47145.1; --			
DR	EMBL; U56855; AAB94794.1; --			

ALIGNMENTS

Q09435 caenorhabdi  
Q08462 homo sapien  
P26770 rattus norv  
P51829 mus musculu  
P26769 rattus norv  
P51828 homo sapien  
Q29450 bos taurus  
O60466 homo sapien  
P21932 rattus norv  
P19754 bos taurus  
P32870 drosophila  
P97490 mus musculu

34 389 10.8 1137 1 CYG1\_C  
35 322.5 9.0 887 1 CYA2\_H  
36 322 9.0 1064 1 CYA4\_RAT  
37 319.5 8.9 1099 1 CYA7\_MOUSE  
38 319 8.9 1090 1 CYA2\_RAT  
39 316 8.8 1080 1 CYA7\_HUMAN  
40 310.5 8.6 1078 1 CYA7\_HUMAN  
41 303.5 8.4 1144 1 CYA3\_BOVIN  
42 303 8.4 1144 1 CYA3\_RAT  
43 302 8.4 1134 1 CYAL\_BOVIN  
44 290.5 8.1 2248 1 CYAL\_DROME  
45 287.5 8.0 1249 1 CYA8\_MOUSE



APPENDIX II

Page 85 of Giuli *et al.* with portions of the sequence that differ from the Gencore database sequence underlined by Applicants.

quences  
3. 1 and  
GC-S $\beta$ ,  
ted mo-  
GC-S $\alpha$ ,

85